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Appendix 1

I hereby certify that the following is a true, correct and
5 accurate translation of the Russian text of RU 2 179 452 C1:

(PAGE 1)

(19) **RU**⁽¹¹⁾ **2 179 452**⁽¹³⁾ **C1**

(51) **IPC**⁽⁷⁾ **A 61 K 38/17, A 61 P 35/00**

10

**RUSSIAN AGENCY
FOR PATENTS AND TRADEMARKS**

(12) **The specification to the patent of the Russian Federation**

15

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20

27.02.1998. RU 2058153 C1, 20.04 1996. RU 2134589 C1,
20.08.1999. RU 2097060 C1, 27.11.1997.

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30

**(54) METHOD OF TREATMENT OF MALIGNANT NEOPLASMS AND COMPLEX
PREPARATION HAVING ANTINEOPLASTIC ACTIVITY FOR USE IN SUCH
TREATMENT**

35

(57) Abstract

The invention relates to medicine, oncology in particular. It

has been proposed, depending on the character and seriousness of the disease, to inject parenterally to a patient, together with the basic infusion-detoxication therapy, the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic, mainly amphotericin B or nystatin, in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler once within twenty-four hours at an interval of three days in a course of 10 infusions. The complex preparation having antineoplastic activity comprises the following components, in mg: AFP 0.07 - 0.15, a polyene antibiotic 4.2 - 7.0 and a filler 3.5 - 5.0. As a filler mainly polysaccharide selected from the group of rheopolyglukin*, polyglukin* or sugar, for example glucose, is used. The method enables to lower the doses of injectable medicines and to reduce the costs of treatment. The complex preparation distinguishes by high efficiency of antineoplastic activity, a small number of components, simplicity of preparation and a long term of storage. 2 independent and 2 dependent claims.

20 (PAGES 3 to 6)

The invention relates to the field of medicine, oncology in particular and can be used for chemotherapeutical treatment of oncological patients, suffering from different kinds of malignant neoplasms.

Methods of treatment of cancer by means of chemical preparations are known. According to mechanism of action chemical preparations are subdivided into alkylating agents, antimetabolites, alkaloids, antibiotics, hormones, immunomodulators and some others. In the course of treatment by different chemical preparations, the advantages and disadvantages thereof have been revealed.

Owing to comparatively small working concentrations, the chemical preparations affecting DNA are widely used. Alkylation of the vital DNA molecule leads to incapability of normal

fission of cells and to their subsequent elimination. However, at the same time, DNA of normal non-cancerous cells is also subjected to alkylation. In order to reduce toxicity in relation to normal cells, when such preparations are applied, the methods for targeted delivery of preparations to cancerous cells by means of specific ligands, for example alpha-fetoprotein (AFP), are used. AFP is a transport protein, capable of delivering the substance bounded thereto to the cells having corresponding receptors. Such receptors abound on actively proliferating cancerous cells.

The method of treatment of primary liver cancer by means of intra-arterial injection of AFP in an amount of 2-20 mg, mainly 15 mg, five times at an interval of 7-12 days is known (Patent RU 2,058,153, cl. A 61 K 38/00, published April 20, 1996, Bull. 11).

The known method foresees the use of large amounts of AFP and distinguishes by long duration and limited extent of use, since the conditions for selecting patients for treatment by such a method are absence of jaundice and ascites, unoperability, absence of serious concurrent diseases.

The method of treatment of malignant neoplasms by means of intravenous injection of a complex preparation, comprising AFP and estrone-doxorubicin conjugate (Patent RU 2,026,688, cl. A 61 K 38/00, published January 20, 1995, Bull. 2), is known. For preparation of the complex preparation impure AFP, an abortive material is used which is concentrated after rough purification to the content of AFP of 100 µg/ml and is then sterilized. Thereafter an antineoplastic antibiotic - doxorubicin is subjected to conjugation with a ligand - estrone in an equimolar ratio. Immediately 1-2 hours before intravenous injection the concentrate of AFP in an amount of 100 ml is mixed with 20 ml of the conjugate and thus one dose of the complex preparation for one injection (a single dose of AFP comprises 10 mg) is

obtained. The overall course of treatment comprises 6 injections (three times every other day at an interval of a week).

The disadvantage of the known method is the use of high doses of AFP, the disadvantage of the known complex preparation is a labour-intensive procedure of obtaining the three-component complex AFP-estrone-doxorubicin and impossibility of storage of the preparation for more than 2 hours.

10 The closest method to the present method (the prototype) is a method of treatment of primary liver cancer, comprising injection of the preparation doxorubicin dissolved in Lipiodol ultrafluid into the liver artery, while as the preparation doxorubicin doxorubicin-estrone dissolved in 96% ethyl alcohol
15 at 70-76°C in a dose of 20-60 mg in 10-15 ml of Lipiodol ultrafluid is used. 20 minutes prior to that a dose of 2-10 mg of AFP in 12-15 ml of physiological salt is injected into the liver artery; the repeated treatment is carried out after 3-4 weeks (Patent RU 2,065,307, cl. A 61 K 38/17, published
20 August 20, 1996, Bull. 23).

The disadvantages of the known method are:

- labour-intensity of the method, connected with separated
25 injection of AFP and of doxorubicin-estrone complex;
- the use of high concentrations of the chemical preparations (AFP - 2-10 mg, doxorubicin-estrone complex - 20-60 mg), which can lead to toxic side reactions;
- high cost of treatment.

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The closest complex preparation to the present complex preparation (the prototype) is a kit used for treatment of primary liver cancer and comprising doxorubicin-estrone in an amount of 20-60 mg in 15 ml vials, Lipiodol ultrafluid in two
35 ampules by 10 ml, AFP in an amount of 2-10 mg in 10 ml vials, physiological salt in volume of 15 ml in an ampule and 96% ethyl

alcohol in volume of 5 ml in an ampule (Patent RU 2,065,307, cl. A 61 K 38/17, published August 20, 1996, Bull. 23).

The disadvantages of the known kit are:

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- labour-intensity and duration of obtaining the sterile doxorubicin-estrone complex as well as labour-intensity of preparation of the working solution of the given preparation: the preparation is dissolved in 0.5-1.5 ml of 96% ethyl alcohol, heating to 70-76°C, the resultant solution is transferred into 10-15 ml of previously upwarmed Lipiodol ultrafluid, the suspension thus obtained is cooled to 32-37°C and is then injected into the liver artery under X-ray television control;
- high concentrations of the preparations used in the kit;
- polycomponent nature of the kit.

The technical object of the group of the inventions is to simplify the known method, to lower the doses of the preparations to be injected and to reduce the costs of treatment.

The established object has been achieved by means of hereby proposed method of treatment of malignant neoplasms and a complex preparation having antineoplastic activity for use in such treatment.

The realization of the method of treatment.

Depending on the character and seriousness of the disease, to a patient, together with the basic infusion-detoxication therapy, the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler, is parenterally injected once within twenty-four hours at an interval of three days in a course of 10 infusions.

The complex preparation having antineoplastic activity comprises the following components, in mg:

AFP	0.07 - 0.15
a polyene antibiotic	4.2 - 7.0
5 a filler	3.5 - 5.0

As a polyene antibiotic amphotericin B or nystatin is mainly used.

- 10 As a filler sugars are mainly used, for example glucose or synthetic polymers, selected from the group of polysaccharides, for example polyglukin, rheopolyglukin and dextran.

The complex preparation is obtained as follows: AFP with purity
 15 not less than 98% is dissolved in distilled water or physiological salt in an amount of 0.07-0.15 mg/ml, whereto a polyene antibiotic in an amount of 4.2-7.0 mg/ml and then a filler in an amount of 3.5-5.0 mg/ml are added, after that the components are carefully mixed and the resultant mixture is
 20 then left to stand at 18-25°C for 10-12 hours. Thereafter the solution is sterilized by filtration, pre-packed in ampules or vials having a capacity of 1.2 or 3 ml and freeze-dried. The mass ratio of AFP, a polyene antibiotic and a filler is 1:(60-100):(50-70).

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The complex preparation (conventional designation Reducin) is a powder of yellow colour, soluble in water, in physiological salt, in glucose solution and in other diluents (carriers), suitable for intravenous injection. One ampule of the complex
 30 preparation comprises: 0.07-0.15 mg of AFP, 4.2-7.0 mg of polyene antibiotic and 3.5-5.0 mg of corresponding filler. For preparation of the working solution the content of the ampule is dissolved in 2-3 ml of sterile water and is then transferred into 200 ml vial together with a carrier, suitable for
 35 intravenous injection.

The present method comprises injection to a patient of a new complex chemical preparation having antineoplastic activity and consisting of a vector part (AFP), specific to cancerous cells, and a nonspecific part, comprising a cytotoxic substance. As the latter an essentially new channel-forming and surface-active agent (SAA), namely a polyene antibiotic, for example amphotericin B or nystatin, which have not been previously used as antineoplastic remedies, is used. The targets for the new complex preparation are membranes of intracellular substructures. Such substructures include mitochondria, lysosomes, endoplasmatic reticula (EPR), nuclei, etc. In case of disorders in the function of membranes of substructures, a normal cell function, ensurable by the compartmentalization of different functions, is impossible. As a result autodigestion of cancerous cells takes place according to the mechanism of induced apoptosis.

The use of AFP as a vector for targeted delivery of cytotoxic preparations to cancerous cells is known (see for instance patent RU 2,071,351, cl. A61 K 38/17, published January 10, 1997). In all known cases AFP is bounded with a cytotoxic part of the preparation by a chemical covalent bond, whereas in the present complex preparation AFP and SAA form a noncovalent complex, ensuring simultaneously the stability of the macromolecule during transportation and its functional independence in the process of cytotoxic action of the polyene antibiotic. The activity of the present complex preparation is based on the initiation of physiological reduction of cancerous cells according to the mechanism similar to that of apoptosis. As a rule, the natural autodestruction of the cells of tumor under the influence of the present complex preparation does not lead to intoxication of the organism and the effect of the treatment appears quickly.

The essential distinctive features of the present method, as compared with those of the prototype, are:

- to a patient the complex preparation, comprising AFP in an amount of 0.07-0.15 mg, a polyene antibiotic in an amount of 4.2-7.0 mg and a pharmaceutically suitable filler, is injected parenterally and simultaneously in a course of 10 injections
5 (infusions) once in three days, which enables to simplify the known method, to lower the doses of the preparations to be injected and to reduce the costs of treatment.

The essential distinctive features of the present complex
10 preparation, as compared with those of the known preparation, are:

- the complex preparation comprises additionally a surface-active agent, namely a polyene antibiotic, mainly amphotericin
15 B or nystatin, in an amount of 4.2-7.0 mg, which provides the complex with a new type of bond with a vector part - with a noncovalent bond, and a new mechanism of interaction with cancerous cells - with the membranes of the substructures of cancerous cells (membranes of lysosomes, EPR, mitochondria,
20 nuclei), which, in its turn, improves the efficiency of the treatment and reduces side complications;
- the complex preparation comprises the components in optimal, experimentally selected amounts and ratios, namely: AFP - 0.07-0.15 mg, a polyene antibiotic - 4.2-7.0 mg, a filler - 3.5-5.0
25 mg, which enables to improve the efficiency of the treatment and substantially lower the doses of the active components used.

Being supported by the fact that no analogous method of treatment of malignant neoplasms and no analogous complex
30 preparation having antineoplastic activity have been revealed, it may be concluded that the present group of inventions meet the requirements for patentability in respect of "novelty" and "inventive step".

35 The present method has been tested on 8 patients having IV clinical stage of oncological diseases, progressing after

traditional ways of treatment. A full or a partial clinical effect has been achieved on 6 patients out of 8 (75%). The terms of remission were from 6 months to 1.5 years. In majority cases, for achieving a well-defined clinical effect it was sufficient to conduct one course of treatment.

The inventions are characterized by the following Examples.

Example 1

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For preparation of the complex preparation Reducin 700 mg of AFP, 42 g of amphotericin B and 50 g of rheopolyglukin are dissolved in 1 litre of distilled water by mixing, subsequently the volume is increased up to 10 litres. The resultant mixture is incubated at room temperature for 10-12 hours and is then subjected to sterilization by filtration through a membrane filter, pre-packed in 10,000 ampules or vials by 1 ml (a single dose) and thereafter freeze-dried in aseptic conditions. One ampule (vial) comprises 0.07 mg of AFP, 4.2 mg of amphotericin B and 5.0 mg of rheopolyglukin.

Example 2

The complex preparation Reducin is obtained analogously to Example 1, with the exception that to water solution 1 g of AFP, 50 g of amphotericin B and 40 g of polyglukin are added. As a result the preparation, comprising 0.1 mg of AFP, 5.0 mg of amphotericin B and 4.0 mg of polyglukin in a single dose, is obtained.

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Example 3

The complex preparation is obtained analogously to Example 1, with the exception that to water solution 1.5 g of AFP, 70 g of amphotericin B and 30 g of dextran (molecular mass 100 kDa, Serva) are added. As a result the preparation, comprising 0.15

mg of AFP, 7.0 mg of amphotericin B and 3.0 mg of dextran in a single dose, is obtained.

Example 4

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The complex preparation is obtained analogously to Example 1, with the exception that to water solution 750 mg of AFP, 60 g of nystatin and 50 g of glucose are added. As a result the preparation, comprising 0.075 mg of AFP, 6.0 mg of nystatin and 10 5.0 mg of glucose in a single dose, is obtained.

Example 5

Patient L., 54 years old, the patient record 587, was 15 hospitalized on April 02, 1999 with the diagnosis: central cancer of the right lung IV stage (recidivation, progressive course), cancer of the left mammary gland II stage (remission). The patient was complaining weakness, dyspnea, exhausting cough.

20 The data of the inspection. X-ray photograph of the organs of thorax: on both sides in the lungs there are numerous polymorphous shadows of metastases in sizes from 0.5 to 2.5 cm and of medium intensity and uneven outlines. The shadow of mediastinum has shifted rightwards and expanded. The right lung 25 field has diminished in volume; below the fourth rib there is an intensive overshadowing because of the liquid in the pleural cavity.

A course of polychemotherapy was conducted according to the 30 scheme CAF: On the 1st and 8th days intravenously 1 g of cyclophosphane, on the 1st and 8th days intravenously 500 mg of 5-fluorouracil, on the 2nd and 9th days of the treatment intravenously 40 mg of adriablastin. The treatment was accompanied by high toxicity without an expressed clinical 35 effect.

Thereafter the patient was treated according to the present method. The complex preparation Reducin, comprising 0.07 mg of AFP, 4.5 mg of amphotericin B and 5.0 mg of glucose, was injected by infusion in a course of 10 injections once in three 5 days. The condition of the patient has improved and became satisfactory a week after the course of treatment had been finished. On the basis of the data of the radiology inspection of the organs of thorax favourable changes were registered, characterized by the decreased number of metastases in the lungs 10 and the weakening of intensity of the shadows of dissemination. The liquid in the pleural cavity was not inspected. Dyspnea on ascent has diminished and cough disappeared completely. During the treatment with Reducin a rise in temperature and a shiver were observed, which were treated with standard preparations.

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Example 6

Patient M., 62 years old, the patient record 800, was hospitalized with the diagnosis: central cancer of the right 20 lung IV stage (adenocarcinoma); spread metastases in head, in the right hemisphere of brain, in neck, in thorax; right-sided carcinomatous pleurisy; chronic deforming bronchitis; pulmonary emphysema; diabetes of the 2nd type; IBO; angina of effort; secondary immunodeficiency, undernourishment, condition after 25 the courses of polychemotherapy.

The treatment program included a course of polychemotherapy according to the scheme CAMF. To the patient were injected 1 g of cyclophosphane on the 1st and 8th days, adriamycin on the 30 1st and 8th days, 50 mg of methotrexate on the 1st and 8th days, 5-fluorouracil on the 2nd and 9th days. The treatment was accompanied by endotoxiosis and an abrupt worsening of the condition of the patient. No positive effects were detected.

35 Because of complicated condition of the patient, to him intravenous infusions of the complex preparation Reducin,

comprising 0.075 mg of AFP, 5.0 mg of nystatin and 5.0 mg of rheopolyglukin in a single dose, in a course of 10 infusions once in three days were prescribed.

56 days after the beginning of the treatment according to the present method the diminishing of the sizes of subcutaneous metastases were noted. By the end of the treatment rapid improvement of the main disease was noted, which became apparent from the twofold reduction of the size of all surface metastatic
10 nodes, the disappearing of pains in the lower jaw, the decreasing of the rate of exudation in the right pleural cavity. Thrice conducted right-sided pleural puncture proved the decreasing of volume of exudate: before the treatment the volume of exudate was
15 the treatment - 20 ml. The improvement of function of central nervous system became apparent from restoration of normal swallowing function, restoration of gripping function of the left hand, clinically corresponding to the reduction of metastasis in the right hemisphere of brain.

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The use of the present method of treatment of malignant neoplasms and the complex preparation having antineoplastic activity, as compared with the known method of treatment and the kit for use in such treatment, enables:

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- to simplify the method of treatment by means of simultaneous parenteral injection of the complex preparation, comprising AFP and cytotoxic SAA in optimal ratios;
- to lower the doses of the used components: AFP 13-140 times,
30 the cytotoxic component 3-14 times;
- to improve the efficiency of treatment by means of using the complex preparation having high specificity to growing cancerous cells and optimal composition of the complex preparation having a long term of storage (two years);
- 35 - to reduce the costs of treatment by means of using a small number of components in the complex preparation and low doses

of the chemical preparations to be used.

Thus, while using the present method of treatment of malignant neoplasms two biological mechanisms are realized. The first of them comprises the targeted delivery of the cytotoxic agent by means of AFP to tumorous cells. The second one comprises the directed destruction of the tumorous cells because of destruction of the intracellular structures, in particular EPR and lysosomes. This may be accompanied by autodigestion of tumorous cells, caused by the enzymes of hydrolysis, comprising in the lysosomes, according to the mechanism of targetably induced apoptosis. The directed reduction affects much less the cells of blood-forming, immune and other constantly growing systems, being often damaged when standard antineoplastic chemotherapy is applied. The present complex preparation Reducin distinguishes by high efficiency of antineoplastic activity, a small number of components, simplicity of preparation and a long term of storage.

Claims:

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1. A method of treatment of malignant neoplasms, comprising injection of alpha-fetoprotein, characterised in that alpha-fetoprotein is injected as a component of the complex preparation comprising additionally a polyene antibiotic and a filler in ratio of 1: (60-100) : (50-70), and the preparation is injected parenterally in a course of 10 injections once in three days.

2. A complex preparation having antineoplastic activity, comprising alpha-fetoprotein, a cytotoxic substance and a filler, characterized in that the preparation comprises a polyene antibiotic as a cytotoxic substance and polysaccharide or sugar as a filler in the following quantitative ratio of the components, in mg:

AFP	0.07 - 0.15
a polyene antibiotic	4.2 - 7.0
a filler	3.5 - 5.0

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3. A complex preparation of claim 2, characterized in that the preparation comprises amphotericin B or nystatin as a polyene antibiotic.

54. A complex preparation of claim 2, characterized in that the preparation comprises polysaccharide, selected from the group consisting of polyglukin, rheopolyglukin and dextran or sugar, mainly glucose as a filler.

10 * Note: In the present translated text the spelling used for the fillers in question is *polyglukin* and *rheopolyglukin*, basing on the respective usage of the terms in the abstract in English formulated (like the abstract in Russian) by the Russian Patent Office.

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Signature:  Milvi Vänikver

Signed this 26th day of July..2004

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(19) RU⁽¹¹⁾ 2 179 452⁽¹³⁾ C1
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РОССИЙСКОЕ АГЕНТСТВО
 ПО ПАТЕНТАМ И ТОВАРНЫМ ЗНАКАМ

(12) ОПИСАНИЕ ИЗОБРЕТЕНИЯ К ПАТЕНТУ РОССИЙСКОЙ ФЕДЕРАЦИИ

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(54) СПОСОБ ЛЕЧЕНИЯ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ И КОМПЛЕКСНЫЙ ПРЕПАРАТ, ОБЛАДАЮЩИЙ ПРОТИВООПУХОЛЕВЫМ ДЕЙСТВИЕМ, ДЛЯ ОСУЩЕСТВЛЕНИЯ СПОСОБА

(57) Реферат:

Изобретение относится к медицине, а именно к онкологии. Предложено в зависимости от характера и тяжести заболевания больному на фоне инфузионно-детоксикационной терапии парентерально вводить комплексный препарат, содержащий АФП в количестве 0,07-0,15 мг, полиеновый антибиотик, преимущественно амфотерицин В или нистатин, в количестве 4,2-7,0 мг и наполнитель, один раз в сутки с интервалом в три дня, курсом 10 инфузионно-капельных вливаний. Комплексный препарат,

обладающий противоопухолевым действием, содержит следующие компоненты, мг: АФП 0,07-0,15, полиеновый антибиотик 4,2-7,0, наполнитель 3,5-5,0. В качестве наполнителя преимущественно используют полисахарид из группы реополиглюкин, полиглюкин или сахар, например глюкозу. Способ позволяет снизить дозы вводимых лекарственных средств и снизить стоимость лечения. Комплексный препарат отличается повышенной эффективностью противоопухолевого действия, малокомпонентностью, простотой получения и длительным сроком хранения, 2 с. и 2 з.п. ф-лы.

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(12) **ABSTRACT OF INVENTION**

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(54) **METHOD TO TREAT MALIGNANT NEOPLASMS AND COMBINED PREPARATION OF ANTITUMOR ACTION TO PERFORM THE METHOD**

(57) Abstract:

FIELD: medicine, oncology. SUBSTANCE: it is suggested as dependent upon character and severity of a disease to inject parenterally a combined AFP-containing preparation at 0.07-0.15 mg, polyenic antibiotic, predominantly amphoterycin B or nistatine at 4.2-7.0 mg and a filler, once daily at 3-d-long interval, at therapy course consisted of 10 infusion-drop injections. Combined preparation of antitumor action

contains the following components, mg: AFP 0.07-0.15, polyenic antibiotic 4.2-7.0, filler 3.5-5.0. As a filler it is predominantly used polysaccharide of rheopolyglukin, polyglukin or sugar group, for example, glucose. EFFECT: decreased doses of injected medicinal preparations and therapy cost, increased efficiency of antitumor action, decreased quantity of components, simplified production and prolonged storage period. 4 cl

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RU 2 179 452 C1

: Ross Fiziol Zh Im I M Sechenova. 1997 Aug;83(8):59-64.

Related Articles, Links

[The effect of the initial (controlled) tonus of the arterial vessels on the correlation of arterial pressure and cardiac output during a pressor reaction to a rapid blood volume increase in rats]

[Article in Russian]

Osadchii LI, Balueva TV, Sergeev IV.

Pavlov Institute of Physiology, Russian Acad. Sci., St. Petersburg, Russia.

A considerable decrease in pressor responses to polyglykine at an elevated arterial tone and constant increase of cardiac output occurred in anesthetised rats. Vascular and cardiac mechanisms of the interrelationship are discussed.

PMID: 9487051 [PubMed - indexed for MEDLINE]

ВЛИЯНИЕ ИСХОДНОГО (УПРАВЛЯЕМОГО) ТОНУСА АРТЕРИАЛЬНЫХ СОСУДОВ НА СООТНОШЕНИЕ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ И СЕРДЕЧНОГО ВЫБОРА ПРИ ПРЕССОРНОЙ РЕАКЦИИ НА БЫСТРОЕ УВЕЛИЧЕНИЕ ОБЪЕМА КРОВИ У КРЫС

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Лаборатория физиологии кровообращения Института физиологии им. И. П. Павлова РАН, Россия, 199034, Санкт-Петербург, наб. Макарова, 6

В опытах на наркотизированных крысах исследовали изменение взаимоотношений между сердечным выбросом и артериальным давлением в процессе формирования прессорной реакции на внутривенное введение 0.5 мл полиглюкина при различном исходном (управляемом ангиотензин-2) тоне артериальных сосудов. Установлено, что на фоне повышенного исходного тонуса (в диапазоне среднего артериального давления от уровня выше 90 до 165 мм рт. ст.) наблюдалось существенное (в 4 раза) уменьшение прессорных эффектов полиглюкина при сохранении в половине наблюдений такого же прироста сердечного выброса, как и на фоне более низкого давления. В основе данной зависимости, по-видимому, лежит сосудистый механизм, связанный с повышением трансмурального давления в артериальной системе.

Ключевые слова: полиглюкин, ангиотензин-II, среднее артериальное давление, сердечный выброс.

L. I. Osadchiy, T. V. Balueva and I. V. Sergeev THE EFFECT OF INITIAL (CONTROLLABLE) TONE OF ARTERIAL VESSELS ON RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND CARDIAC OUTPUT DURING PRESSURE RESPONSES TO A FAST INCREASE IN THE BLOOD VOLUME. Pavlov Institute of Physiology of the Russian Acad. Sci., 199034, St. Petersburg, Nab. Makarova, 6, Russia.

A considerable decrease in pressor responses to polyglutamine at an elevated arterial tone and constant increase of cardiac output occurred in anesthetized rats. Vascular and cardiac mechanisms of the interrelationship are discussed.

Key words: polyglutamine, angiotensin-2, arterial pressure, cardiac output.

В предыдущих исследованиях нами была установлена обратная прямая зависимость между величиной прессорных реакций, вызываемых быстрым введением плазмозаменивателя (полиглюкина) и агониста α -адренорецепторов, от исходного спонтанного [1] и управляемого [2] тонуса артериальных сосудов у крыс. Интерес к этой проблеме усиливается в связи с исследованиями, выполненными под руководством Г. П. Конради, в которых установлена зависимость местных реакций в различных сосудистых областях от величины исходного тонуса сосудов [3]. Кроме того, обнаружены влияния трансмурального давления и нейрогуморального компонента тонуса на вазомоторные реакции сосудов конечности у крыс [4,5,6] и лягушек [7]. Исследований по данной проблеме, выполненных на системном уровне, в доступной литературе нами не обнаружено.

Нами [8] было выдвинуто предположение о том, что, во-первых, повышение исходного тонуса артериальных сосудов неизбежно ведет к увеличению постнагрузки на сердце, в связи с чем прессорную реакцию от введения полиглюкина можно рассматривать как дополнительную постнагрузку, что может влиять на величину сердечного выброса [9]. Во-вторых, в этих реакциях возможно участие сосудистого

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- [18] Stonehouse M. A., Savard G. K. Vagal cardiac baroreflex activity in humans: spontaneous versus carotid-cardiac responses. *Can. J. Physiol. Pharmacol.* 71 (2) : 21. 1993.

Поступила 14 X 1996

> Поиск препаратов > Все препараты ТН > Описание препарата

Полиглюкин сухой

субст.-пор. 1,5 кг; бан. 3 л; №71/609/31; произв.: Биохимик (Россия); код EAN:4602509005225

Уважаемые пользователи!

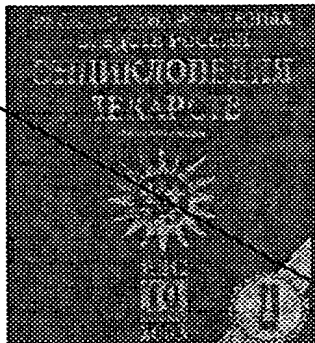
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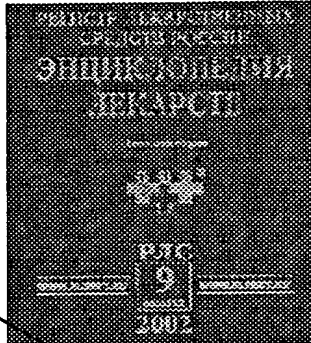
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лекарств 2002 года

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[Результаты анкеты](#)

Appendix 6A

Латинское название: Polyglucinum siccum

Действующее вещество: Декстран* (Dextran*)

Фармакологические группы: Детоксирующие средства, включая антидоты. Заменители плазмы и других компонентов крови

Срок годности: 7 лет

Условия хранения: При температуре от -10 до 20 °C

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Appendix 6B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on appendix 6A, a web site of the register of medicinal agents of Russia:(rls), and that the paragraphs not translated are not relevant.

Polyglucin* dry

substance, powder 1.5 kg; a jar of 3 l; No.71/609/31; producer: Biohimik (Russia); code
EAN: 4602509005225

Name in Latin: Polyglucinum siccum

Active substance: Dextran

Pharmacological groups: Detoxicating agents, including antidotes. Substitutes of plasma and other blood components.

Term of validity: 7 years

Conditions of storage: At temperature of 10-25°C

* Note: The spelling in English, being in line with the given spelling in Latin.

Signature:  Milvi Vänikver

Signed this 26th day of July 2004

> Поиск препаратов > Все препараты ТН > Описание препарата

Реополиглюкин сухой

субст.-пор.; бан. 1 кг; №79/702/2; произв.: Красфарма (Россия); код
EAN:4602521000987

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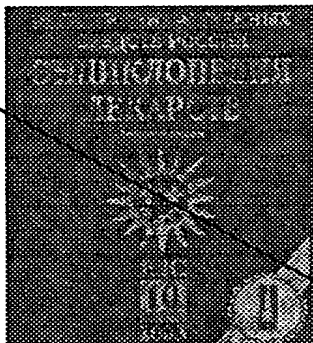
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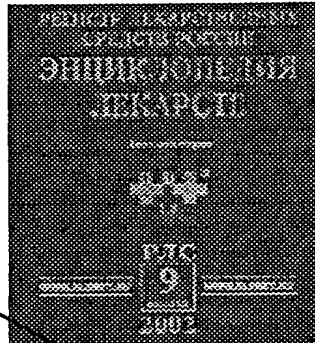
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☐ Да

[Проголосовать](#)

[Результаты анкеты](#)

Appendix 7A

Латинское название: Rheopoluglucinum siccum

Действующее вещество: Декстран* (Dextran*)

Фармакологические группы: Детоксирующие средства, включая антидоты. Заменители плазмы и других компонентов крови

Срок годности: 5 лет

Условия хранения: В сухом месте, при температуре 10-25 °C

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Appendix 7B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on appendix 7A, a web site of the register of medicinal agents of Russia:(rls), and that the paragraphs not translated are not relevant.

Rheopolyglucin* dry

substance, powder; a jar of 1.5 kg; No. 79/702/2; producer: Biohimik (Russia); code
EAN: 4602509005249

Name in Latin: Rheopolyglucinum siccum

Active substance: Dextran

Pharmacological groups: Detoxicating agents, including antidotes. Substitutes of plasma and other blood components.

Term of validity: 5 years

Conditions of storage: In dry place at temperature of 10-25°C

* Note: The spelling in English, being in line with the given spelling in Latin.

Signature:  Milvi Vänikver

Signed this 26th day of July 2004



Appendix 8A, page 1


Recipe.Ru: фармацевтический информационный сайт							В Избранное! Сделать стартовой!
Начало	Списки: Лексредства ; Фирмы ; Страны ; Фармакологическая группа ; Состав по компонентам						
О проекте	Коды ТН ВЭД СНГ ; Фармакологическое действие ;						
Новости	Классификаторы: Фармакологическая группа по АТК ; Лекарственная форма ; Форма выпуска						
Документы	Раздел базы ; Показания по МКБ ;						
Ссылки	Расширенный поиск						
Литература	Вернуться к списку						
Магазин CD	Международное название	Торговое название	Страна-производитель	Фирма-производитель	Номер регистрации препарата	Формы выпуска	
Программы	Декстран, средняя						
Прайс-листы	Декстран, средняя						
Ресурсы	молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	Россия	Не указано	71/609/31	субстанция-порошок аморфный (банки 10 л)	Отобразить
Поиск							
Услуги							
Форумы							
Подписка	Декстран, средняя						
Гостевая книга	молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	Россия	Не указано	71/609/31	субстанция-порошок аморфный (банки 3 л)	Отобразить
Обратная связь							
E-mail	Декстран, средняя						
	молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	Россия	Не указано	71/609/31	субстанция-порошок аморфный (банки 5 л)	Отобразить
	Декстран, средняя						
	молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	Россия	Биохимик ОАО (Саранск)	71/609/31	субстанция-порошок аморфный (банки 10 л)	Отобразить
	Декстран, средняя						
	молекулярная масса 50000-70000 (Dextran, average molecular weight 50000-70000)	Полиглюкин сухой (Polyglucin siccum)	Россия	Биохимик ОАО (Саранск)	71/609/31	субстанция-порошок аморфный (банки 3 л)	Отобразить
	Декстран, средняя						

СОСТАВ ПО КОМПОНЕНТАМ
декстран

Appendix 8A, page 3

Script version: 1.0.0-RC

Recipe.Ru | Идея и дизайн: Дмитрий Шкатов (с) 1999-2004

E-mail |  ICQ | Вверх

Начало | Новости | Прайс-листы | Документы | Литература | Ресурсы | Услуги | Программы | Заказ CD | Ссылки |
Форумы | Подписка



Реклама на www.recipe.ru

Appendix 8B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on pages 1-3 of appendix 8A, the web sites of Recipe.ru: pharmaceutical informational site, and that the paragraphs thereof not translated are not relevant.

Recipe.Ru: Pharmaceutical informational site

International name	Trade name	Country-producer	The firm-producer	Preparation registration number	Output form
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	not indicated	71/609/31	substance-amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	not indicated	71/609/31	substance-amorphous powder (jars of 3 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	not indicated	71/609/31	substance-amorphous powder (jars of 5 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	Biohimik (Saransk)	71/609/31	substance-amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	Biohimik (Saransk)	71/609/31	substance-amorphous powder (jars of 3 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia-	Biohimik (Saransk)	71/609/31	substance-amorphous powder (jars of 5 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	Kraspharma	71/609/31	substance-amorphous powder (jars of 10 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	Kraspharma	71/609/31	substance-amorphous powder (jars of 3 l)
Dextran, average molecular weight 50000-70000	Polyglucin dry (Polyglucin siccum)	Russia	Kraspharma	71/609/31	substance-amorphous powder (jars of 5 l)

Polyglucin dry (Polyglucin siccum*)

International name

Dextran, average molecular weight 50000-70000

Trade name

Polyglucin dry (Polyglucin siccum*)

Country-producer

Russia

Preparation registration number

71/609/31

Output form

substance - amorphous powder (jars of 10 l)

Pharmacological group

plasma substituter

Pharmacological group according to ATC**

B05AA05 Dextran

Pharmacological effect

filling to CBV***

antiaggregative

antishock effect

plasma substituting

desintoxicating

Codes****

2940 00 900 0

3002 90 100 0

Composition from the text of the main table

Dextran, average molecular weight 50000-70000, page 1

Medicinal form

substance - amorphous powder

Output form

jars

Section of the base

Substances, standard examples of medicinal agents and auxiliary substances

Composition according to the components

Dextran

Notes:

* The English translation in the brackets is incorrect because the first word *Polyglucin* is in English whereas the second word *siccum* is in Latin

** ATC - the anatomical therapeutic chemical classification

*** CBV - circulating blood volume

**** Codes in Russian, not relevant

Signature:  Milvi Vänikver

Signed this 26th day of July 2004



30/07/2004 Михаил Зурабов: Бесплатную медицину в России никто не отменит

Appendix 9A, page 1

Recipe.Ru: фармацевтический информационный сайт

В
Избранное!
| Сделай
стартовой!

Начало	Списки: Лексредства ; Фирмы ; Страны ; Фармакологическая группа ; Состав по компонентам ; К					
О проекте	ТН ВЭД СНГ ; Фармакологическое действие ;					
Новости	Классификаторы: Фармакологическая группа по АТК ; Лекарственная форма ; Форма выпуска ; Раз					
Документы	базы ; Показания по МКБ ;					
Ссылки	Расширенный поиск					
Литература	Вернуться к списку					
Магазин CD	Международное название	Торговое название	Страна-производитель	Фирма-производитель	Номер регистрации препарата	Формы выпуска
Программы	Декстран, средняя	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Не указано	79/702/2	субстанция-порошок аморфный (банки 3 л) 300-500 г/л
Прайс-листы	молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)					Отобраз
Ресурсы	Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Не указано	79/702/2	субстанция-порошок аморфный (банки 5 л) 300-500 г/л
Поиск						Отобраз
Услуги						
Форумы						
Подписка						
Гостевая книга						
Обратная связь						
E-mail						
	Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Не указано	79/702/2	субстанция-порошок аморфный (банки 10 л) 300-500 г/л
	Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Биохимик ОАО (Саранск)	79/702/2	субстанция-порошок аморфный (банки 3 л) 300-500 г/л
	Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Биохимик ОАО (Саранск)	79/702/2	субстанция-порошок аморфный (банки 5 л) 300-500 г/л
	Декстран, средняя					субстанция-

Appendix 9A, page 2

молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Биохимик ОАО (Саранск)	79/702/2	порошок аморфный (банки 10 л) 300-500 г/л	Отобраз
Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Красфарма ОАО	79/702/2	субстанция-порошок аморфный (банки 3 л) 300-500 г/л	Отобраз
Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Красфарма ОАО	79/702/2	субстанция-порошок аморфный (банки 5 л) 300-500 г/л	Отобраз
Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000) Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)	Реополиглюкин сухой (Rheopolyglukin siccum)	Россия	Красфарма ОАО	79/702/2	субстанция-порошок аморфный (банки 10 л) 300-500 г/л	Отобраз

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Версия для печ

Реополиглюкин сухой (Rheopolyglukin siccum)**МЕЖДУНАРОДНОЕ НАЗВАНИЕ**

Декстран, средняя молекулярная масса 30000-40000 (Dextran, average molecular weight 30000-40000)

ТОРГОВОЕ НАЗВАНИЕ

Реополиглюкин сухой (Rheopolyglukin siccum)

СТРАНА-ПРОИЗВОДИТЕЛЬ

Россия

НОМЕР РЕГИСТРАЦИИ ПРЕПАРАТА

79/702/2

ФОРМЫ ВЫПУСКА

субстанция-порошок аморфный (банки 3 л) 300-500 г/л

ФАРМАКОЛОГИЧЕСКАЯ ГРУППА

плазмозамещающее средство

ФАРМАКОЛОГИЧЕСКАЯ ГРУППА ПО АТК

B05AA05 Декстран (Dextran)

ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ

восполняющее ОЦК
 антиагрегантное
 противошоковое
 плазмозамещающее
 дезинтоксикационное

КОДЫ ТН ВЭД СНГ

2940 00 900 0
 3002 90 100 0

INGREDIENTTEXT ИЗ ОСНОВНОЙ ТАБЛИЦЫ

декстран, средняя молекулярная масса 30-40 тыс. - 1 л

ЛЕКАРСТВЕННАЯ ФОРМА

субстанция - порошок аморфный

ФОРМА ВЫПУСКА

банки

РАЗДЕЛ БАЗЫ

Субстанции, стандартные образцы лекарственных средств и вспомогательные вещества

СОСТАВ ПО КОМПОНЕНТАМ

декстран

Appendix 9A, page 3**ОПИСАНИЕ**

Белый аморфный порошок без запаха. Реополиглюкин сухой представляет собой полисахариддекстра с молекулярным весом 30 000 — 40 000 и предназначается для приготовления препарата реополиглюкина.

УСЛОВИЯ ХРАНЕНИЯ


В сухом месте при температуре не ниже +10град.С и не выше +25град.С.

СРОК ГОДНОСТИ

4 года.

Script version: 1.0.0

Recipe.Ru | Идея и дизайн: Дмитрий Шкатов (с) 1999-2004

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Appendix 9B

I hereby certify that the following is a true, correct and accurate translation of the essential paragraphs indicated on pages 1-3 of appendix 9A, the web sites of Recipe.ru: pharmaceutical informational site, and that the paragraphs thereof not translated are not relevant.

Recipe.Ru: Pharmaceutical informational site

International name	Trade name	Country-producer	The firm-producer	Preparation registration number	Output form
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	not indicated	79/702/2	substance-amorphous powder (jars of 3 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	not indicated	79/702/2	substance-amorphous powder (jars of 5 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	not indicated	79/702/2	substance-amorphous powder (jars of 10 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance-amorphous powder (jars of 3 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance-amorphous powder (jars of 5 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Biohimik (Saransk)	79/702/2	substance-amorphous powder (jars of 10 l) 300-500 g/l
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Kraspharma	79/702/2	substance-amorphous powder (jars of 3 l)

Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Kraspharma	79/702/2	300-500 g/l substance-amorphous powder (jars of 5 l)
Dextran, average molecular weight 30000-40000	Rheopolyglucin dry (Rheopolyglukin siccum)	Russia	Kraspharma	79/702/2	300-500 g/l substance-amorphous powder (jars of 10 l)

Rheopolyglucin dry (Rheopolyglukin siccum*)

International name

Dextran, average molecular weight 30000-40000

Trade name

Rheopolyglucin dry (Rheopolyglukin siccum*)

Country-producer

Russia

Preparation registration number

79/702/2

Output form

substance - amorphous powder (jars of 3 l), 300-500 g/l

Pharmacological group

plasma substituter

Pharmacological group according to ATC**

B05AA05 Dextran

Pharmacological effect

filling to CBV***

antiaggregative

antishock effect

plasma substituting

desintoxicating

Codes****

2940 00 900 0

3002 90 100 0

Composition from the text of the main table

Dextran, average molecular weight 30000-40000, page 1

Medicinal form

substance - amorphous powder

Output form

jars

Section of the base

Substances, standard examples of medicinal agents and auxiliary substances

Composition according to the components

Dextran

Description

White amorphous odourless powder. Dry rheopolyglucin is a polysaccharide dextran of molecular weight 30000-40000 and is intended for the preparation of rheopolyglucin solution.

Conditions of storage

In dry place at temperature of not less than 10°C and not higher than 25°C.

Term of validity

4 years

Notes:

- * The English translation in the brackets is incorrect because the first word *Rheopolyglukin* is in English whereas the second word *siccum* is in Latin.
- ** ATC - the anatomical therapeutic chemical classification
- *** CBV - circulating blood volume
- **** Codes in Russian, not relevant

Signature:  Milvi Vänikver

Signed this 26th day of July 2004

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